



Health-related quality of life 14 years after preoperative short-term radiotherapy and total mesorectal excision for rectal cancer: Report of a multicenter randomised trial[☆]



Lisette M. Wiltink^a, Tina Y.T. Chen^d, Remi A. Nout^a,
Elma Meershoek-Klein Kranenbarg^b, Marta Fiocco^c, Søren Laurberg^d,
Cornelis J.H. van de Velde^b, Corrie A.M. Marijnen^{a,*}

^a Department of Clinical Oncology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands

^b Department of Surgery, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands

^c Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands

^d Department of Surgery P, Aarhus University Hospital, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark

Received 24 June 2014; accepted 30 June 2014

Available online 21 July 2014

KEYWORDS

Quality of life
Mesorectal
Rectal
Randomised trial
Very long-term follow-up

Abstract Background: Preoperative short-term radiotherapy (PRT) in combination with total mesorectal excision (TME) has shown to improve local control in rectal cancer treatment, however without a survival benefit and at the cost of increased morbidity. The current study investigates the long-term health-related quality of life (HRQL) of patients 14 years after treatment in the Dutch TME trial.

Methods: In the TME trial (1996–1999) 1530 Dutch patients with rectal cancer were treated with TME and randomly assigned to PRT (5 × 5 Gy). In 2012 HRQL was evaluated in surviving patients ($n = 606$) using a questionnaire combining EORTC QLQ-C30, EORTC QLQ-CR29 and additional questions.

Findings: Results were obtained from 478 patients (82%), with a median follow up of 14 years. PRT + TME patients without stoma reported more faecal leakage and higher stool frequency, resulting in increased need of pads. Furthermore, irradiated males reported more erection problems. However, radiotherapy did not have negative effects on overall functioning. Compared with Dutch population, patients in both treatment arms reported a small decrease in overall functioning and males reported less sexual activity, interest and enjoyment and more

Presented at: the European Cancer Congress 2013, Amsterdam, The Netherlands, 27th of September–1st of October, 2013.

* Corresponding author: Address: Department of Clinical Oncology, K1-P Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 (0) 71 526 5539; fax: +31 (0) 71 526 6760.

E-mail address: marijnen@lumc.nl (C.A.M. Marijnen).

<http://dx.doi.org/10.1016/j.ejca.2014.06.020>

0959-8049/© 2014 Elsevier Ltd. All rights reserved.

erection difficulties. Irradiated females reported more vaginal dryness and more pain at intercourse compared with Dutch population.

Interpretation: Long-term HRQL evaluation shows that treatment-related symptoms are still present 14 years after treatment for rectal cancer. Radiotherapy increased bowel dysfunction in patients without stoma. Compared with the Dutch population, both groups reported increased sexual dysfunction. Despite these treatment-related symptoms, there was no difference in overall functioning and global health between TME and PRT + TME.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

Local recurrence used to be a major problem in rectal cancer treatment. With the introduction of total mesorectal excision (TME) over the last decades an improved local control and survival has been achieved [1]. Several randomised trials found an additional benefit in local control after preoperative radiotherapy (PRT) [2–4]. The Dutch TME trial was one of these trials in which 1861 patients were randomly allocated between short-term preoperative radiotherapy followed by TME surgery or TME alone. Local recurrence after TME was 11% at 10 years, compared to 5% after PRT + TME. Despite this improvement in local control, there was no benefit in overall survival (TME: 49%, PRT + TME: 48% at 10 years) and PRT was associated with increased treatment-related morbidity [5,6].

Due to the growing number of long-term rectal cancer survivors, together with the increased life expectancy, long-term treatment-related morbidity and its effects on health-related quality of life (HRQL) have become an important issue. Previous studies found that at 5 years after treatment, irradiated rectal cancer patients developed more bowel and sexual dysfunction compared with non-irradiated patients [6–8]. Few studies investigated HRQL of rectal cancer survivors with longer follow-up. More bowel dysfunction and hospital admissions for bowel obstruction in irradiated patients have been reported up to 10 years after diagnosis [9–12]. The aim of this analysis was to evaluate the very long-term HRQL of patients treated in the Dutch TME trial still alive more than 12 years after diagnosis.

2. Patients and methods

2.1. Study population and treatment

From January 1996 until December 1999, 1861 patients with resectable rectal cancer were randomly assigned to PRT followed by standardised TME surgery or TME alone in a large, international, multicentre trial. Patients were eligible if they had clinically resectable rectal adenocarcinoma without evidence of distant metastases.

The inferior margin of the tumour had to be located below the level of S1/S2 and not further than 15 cm from

the anal verge. In order to participate in the trial all patients had to give informed consent before randomisation. The design of the trial is approved by the ethics committee and has been reported in previous studies [2,6].

Both radiotherapy and surgical procedures have been reported in detail previously as well [2,6]. For radiotherapy, patients were treated with a total dose of 25 Gy in five fractions over 5–7 days delivered with a three or four-field technique. The clinical target volume included the primary tumour and the mesentery containing the perirectal, presacral and internal iliac nodes up to the S1/S2 junction. If an abdominoperineal resection (APR) was planned, the perineum was included in the clinical target volume, otherwise the lower field border was 3 cm above the anal verge. All patients underwent surgery according to the TME principles [2,6].

HRQL was evaluated in all surviving Dutch patients of the TME trial. To check the survival status of the patients, information provided by the Central Bureau of Genealogy and by patients' general practitioners was used. In July 2012 HRQL questionnaires were sent to all surviving patients, except for patients who had declined participation in the last questionnaire sent in the TME trial. Patients who did not respond initially were sent one reminder.

2.2. Measurements

The HRQL questionnaire was composed of the cancer specific European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC QLQ-C30) [13] and the colorectal module (EORTC QLQ-CR29) [14]. Because only a few questions about sexuality are included in the EORTC QLQ-CR29, sexuality items from the previous colorectal module (EORTC-CR38) [15] and items from prostate (EORTC QLQ-PR25) [16] and cervical cancer (EORTC QLQ-CX24) [17] modules were included. For most questions four-point Likert-type scales were used. All individual-item responses and subscales were linearly converted to 0–100 scales. Higher scores for functioning represent a better level of functioning. For the symptom items, a higher score reflects a higher level of symptoms and therefore decreased HRQL.

In 2003 late morbidity of surviving Dutch patients of the TME trial was assessed using a questionnaire that

contained items about bowel function, stoma function, urinary function, impact of bowel and urinary dysfunction, and level of satisfaction with bowel, stoma and urinary function. Questions were also asked about pain in the back, buttock, legs and hips, stiffness of the hip, walking difficulties, the use of walking aids and co morbidities [6]. In order to acquire more detailed information these additional questions were included in the current questionnaire and scores were transformed into binary outcome measures (i.e., only ‘no’ was no, all other scores were considered as yes).

2.3. Statistics

All data were analysed with IBM SPSS Statistics, version 20.0. To compare characteristics between the treatment groups the independent *t* test was used for continuous variables and the χ^2 test for categorical variables. HRQL analysis and handling of missing values were done according to the guidelines provided by the EORTC Quality of Life Group [18]. Mean scores of the treatment groups were compared using the Mann–Whitney *U* test. For categorical items the χ^2 test was used. Data from the Dutch norm population [19] were matched for age and gender and compared with both treatment groups by a linear regression model. Norm data were available for the EORTC QLQ-C30 and for questions about sexuality [19].

All patients who provided information about sexual symptoms were included in the sexual analyses. To guard against false-positive results due to multiple testing, a two-sided *P* value of .01 was considered statistically significant. Differences in mean scores were interpreted as clinically relevant but small, if the differences were between five and 10 points on a scale of

100 points. A difference between 10 and 20 points was indicated as moderate and a difference greater than 20 points was interpreted as large [20].

2.4. Role of the funding source

The funding sources did not have any role in the data collection, analysis, interpretation or writing of the manuscript.

3. Results

3.1. Study population and compliance

Of 1530 Dutch study patients, 606 were still alive in July 2012. Nineteen patients refused further participation on a previous questionnaire in 2003 and four patients were untraceable, leaving 583 patients who were sent a HRQL questionnaire (Fig. 1).

Of these, 478 returned the questionnaire, resulting in a response rate of 82%. Among the responders, one TME patient received chemo radiation and one TME patient received postoperative 30 Gy instead of 50.4 Gy, and 10 TME patients received post-operative chemotherapy. In the PRT + TME group, 14 patients received a total dose less than 25 Gy, and 11 patients received additional chemotherapy. The median follow-up time since surgery was 14 years for the responders, and 15 years for the non-responders (range 12–17 years). Patient characteristics are equally balanced between responders and non-responders (table 1).

Overall, the treatment groups did not differ significantly with regard to questionnaire response rates and missing items. Questionnaires were complete for all items of the EORTC QLQ-C30 in 82.2% of the responders,

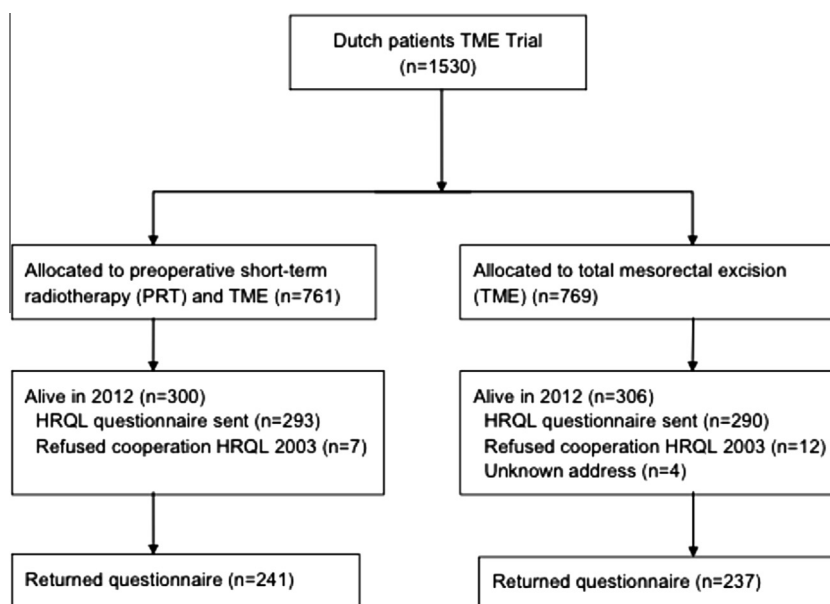


Fig. 1. CONSORT diagram of study patients.

Table 1
Patient characteristics for the HRQL responders and non-responders.

Characteristics	Responders				<i>P</i>	Non-responders		<i>P</i> [‡]
	PRT + TME (<i>n</i> = 241)		TME (<i>n</i> = 237)			(<i>n</i> = 105)		
	No. of patients	%	No. of patients	%		No. of patients	%	
<i>Age, years</i>					.04			.57
Median	77		74			75		
Range	43–95		39–93			42–97		
<i>Sex</i>					.12			.34
Male	150	62.2	131	55.3		67	63.8	
Female	91	37.8	106	44.7		38	36.2	
<i>TNM stage</i>					.29			.76
0	6	2.5	9	3.8		3	2.9	
I	104	43.1	95	40.1		46	43.8	
II	64	26.6	68	28.7		25	23.8	
III	64	26.6	65	27.4		31	29.5	
IV	3	1.2	0	0		0	0	
<i>Distance to anal verge, cm</i> [*]					.71			.91
0–5	70	29.2	76	32.2		34	32.4	
05–10	97	40.4	95	40.3		40	38.1	
10–15	73	30.4	65	27.5		31	29.5	
<i>Operation type</i>					.48			.43
LAR	158	65.6	164	69.2		72	68.6	
APR	74	30.7	68	28.7		27	25.7	
Hartmann	9	3.7	5	2.1		5	4.8	
Other	0	0	0	0		1	1.0	
<i>Stoma present</i>					.34			.09
Yes	107	44.4	95	40.1		35	33.3	
No	134	55.6	142	59.9		70	66.6	

Abbreviations: HRQL, health-related quality of life; PRT, preoperative short-term radiotherapy; TME, total mesorectal excision; LAR, low anterior resection; APR, abdominoperineal resection.

^{*} Difference between treatment arms.

[‡] Difference between responders and non-responders.

^{*} For one irradiated patient and one non-irradiated patient, tumour location could not be determined.

in 76.6% for the EORTC QLQ-CR29 without sexual items and in 59.8% for all questions used in the 2003 HRQL analysis. When allowing up to two missing items, these rates were 95.1%, 92.4%, and 84.6% respectively. Sexually active women (29.9%) completed all sexual items in 84.7%, and sexually active men (40.9%) completed all sexual items in 91.3%. Non-irradiated patients were slightly younger than irradiated patients (median age 74 years in TME versus 77 years in PRT + TME; $P = .04$), but all other patient characteristics were well balanced between the treatment arms (Table 1).

3.2. Patient functioning

No significant differences in mean scores of EORTC QLQ-C30 functioning scales and global health status were found between the treatment arms. However, compared with the Dutch population both treatment groups reported lower mean scores for emotional, cognitive, and social functioning. All differences were small in terms of clinical relevance. The PRT + TME patients also reported a small decrease in physical functioning

compared with the Dutch population (difference -5.9 points, $P < .001$; table 2 and Fig. 2A).

3.3. Symptoms

While there were no differences in bowel symptoms between treatment groups in patients with a stoma, more PRT + TME patients without stoma had an increase in stool frequency (mean PRT + TME 26.3 versus TME 19.4); this difference is mainly explained by more PRT + TME patients reporting the response option a little (during the day, PRT + TME 41.4% versus TME 28.6%). Furthermore, TME patients had less faecal leakage (72.6% not at all after TME compared to 54.3% after PRT + TME, Table 3) and less urge for defecation, less defecation within 1 h of the last bowel opening, and less anal mucus loss, leading to lower frequency of use of pads for faecal leakage (Table 4). No significant differences were found in urinary function between the treatment arms (Table 4). Furthermore, no differences were reported in pain in the back, buttock, legs and hips, and in use of walking aids between the treatment arms. However, a trend was shown towards an increase in walking difficulties after

Table 2
Patient functioning scores and symptom scores of EORTC QLQ-C30.

	Mean score PRT ± TME	Mean score TME	<i>P</i> [*]	Δ PRT ± TME – Norm	<i>P</i> [‡]	Δ TME – Norm	<i>P</i> [•]
Global health status	77.2	78.5	.16	1.4	.29	2.6	.05
<i>Functional scales</i>							
Physical functioning	77.5	80.9	.08	–5.9	<.001	–2.9	.01
Role functioning	79.4	81.4	.30	–4.1	.01	–2.5	.14
Emotional functioning	86.1	85.8	.35	–3.5	.006	–3.3	.009
Cognitive functioning	83.3	84.0	.33	–5.7	<.001	–5.1	<.001
Social functioning	86.8	87.7	.59	–5.2	<.001	–4.4	<.001
<i>Symptom items</i>							
Fatigue	24.9	23.1	.62	5.8	<.001	3.8	.01
Nausea and vomiting	2.7	2.3	.83	.4	.65	0	.91
Pain symptoms	13.1	12.4	.43	–7	<.001	–7.6	<.001
Dyspnoea	14.1	14.3	.78	3.5	0.01	3.6	.008
Insomnia	18.1	23.6	.03	1.6	.35	6.3	<.001
Appetite loss	6.8	5.5	.44	2.9	.005	1.5	.15
Constipation	10.8	13.4	.43	3.9	.001	6.6	<.001
Diarrhoea	11	10.6	.89	6.9	<.001	6.7	<.001
Financial difficulties	5.5	4.9	.66	2.1	.04	1.5	.13

Higher scores for functioning indicate better functioning. For the symptom items, a higher score reflects a higher level of symptoms and decreased HRQL. A negative difference in functioning indicates worse functioning in the treatment arms and a positive difference for symptoms indicates a higher level of symptoms in the treatment arms compared to Norm.

Abbreviations: PRT, preoperative short-term radiotherapy; TME, total mesorectal excision; Norm, age and gender matched Dutch population.

* Difference between PRT + TME and TME.

‡ Difference between PRT + TME and Norm.

• Difference between TME and Norm.

PRT + TME (53.9% after PRT + TME compared to 40.5% after TME, $P = .02$). Compared with the Dutch population, differences in mean scores of EORTC QLQ-C30 symptoms were found. Patients in both treatment arms indicated more fatigue, dyspnoea, insomnia, appetite loss, constipation, and diarrhoea, while indicating less pain. However, all these differences were small in terms of clinical relevance (Table 2, Fig. 2B and C).

3.4. Sexual functioning

Of all males, 40.9% reported to be sexually active. A significant increase was found in erection difficulties in the irradiated group (50.5% very much after PRT + TME compared to 29.8% very much after TME). Compared with the Dutch population, both males treated with PRT + TME or TME alone reported significantly less interest in sex, less sexual activity, less enjoyment of sex, and more erection difficulties: the difference in erection difficulties is large, whereas the difference in sexual interest is moderate in terms of clinical relevance (Table 5, Fig. 2D and E).

Of all females, 29.9% reported to be sexually active. Irradiated females reported a trend towards more pain during intercourse (7.5% quite a bit and 12.5% very much after PRT + TME compared to 0% and 5.4% respectively after TME), and decreased extent to which sex was enjoyable. Compared with the Dutch population, irradiated females reported a significant, clinically large difference in enjoyment of sex and pain during intercourse, and a clinically moderate difference in

vaginal dryness, whereas this was not found in non-irradiated females. In addition, irradiated females reported a clinically large decrease in extent of enjoyment of sex, and non-irradiated females a small decrease compared with the Dutch population (Table 5, Fig. 2D and E).

4. Discussion

This analysis of patient-reported HRQL in the Dutch TME trial shows that treatment-related symptoms are still present at 14 years after treatment for rectal cancer, while overall patient functioning and global health are similar between the treatment groups. After PRT + TME, patients without stoma reported increased bowel dysfunction compared with TME. Compared with the Dutch population, both treatment groups reported increased sexual dysfunction and a small decrease in quality of life.

Our results provide unique information about the very long-term HRQL of patients treated for rectal cancer using validated questionnaires with a high response rate (82%). To our knowledge, only one study reported HRQL of rectal cancer survivors after more than 10 years [12] and three observational studies reported long-term anorectal and colorectal function after 10 years [9,21,22]. However, patients included in these studies did not undergo surgery according to the TME technique and in two studies patients underwent postoperative radiotherapy instead of preoperative radiotherapy [21,22]. Moreover, HRQL of both treatment arms

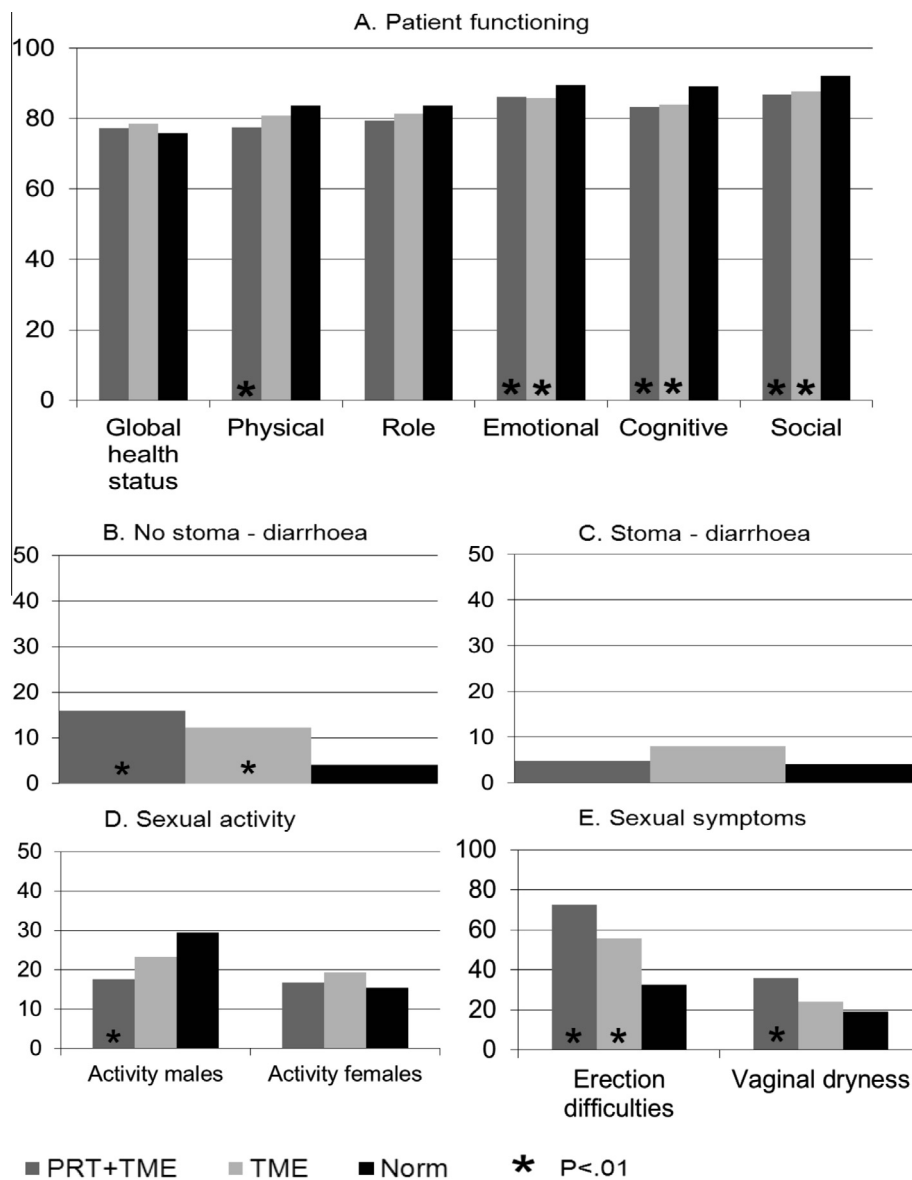


Fig. 2. Mean scores of treatment arms compared to the mean scores of the Dutch population. *Abbreviations:* PRT, preoperative short-term radiotherapy; TME, total mesorectal excision; Norm, age and gender matched Dutch population. Higher scores for functioning indicate better functioning. For the symptom items, a higher score reflects a higher level of symptoms and decreased HRQL.

in our study was compared to age and sex matched Dutch population data.

Our present findings are consistent with the previous reported findings of increased bowel dysfunction after PRT + TME at 2 and 5 years after treatment in this trial [6,23]. The data are also in line with other studies that reported long-term bowel dysfunction [9,10]. In a study that included 340 patients of the Eindhoven Cancer Registry up to 10 years after treatment, more gastrointestinal and defecation problems (EORTC QLQ-CR38) were found after PRT + TME compared with patients who only underwent surgery [11]. In the Stockholm trials patients underwent surgery and PRT or surgery alone, and HRQL of 139 rectal cancer survivors was assessed 15 years after treatment. In the Stockholm

trials, patients who underwent PRT and anterior resection, reported more faecal incontinence compared to the surgery only patients (57.1% after PRT + surgery versus 26.2% after surgery alone) [12]. Bowel dysfunction can be caused by different mechanisms. First, muscles of the pelvic floor can be impaired by fibrosis caused by radiotherapy, resulting in a weaker pelvic floor and a weakening of the anal sphincter and therefore in more faecal leakage. Second, the myenteric plexus in the internal anal sphincter can be damaged due to PRT, which impairs impulse conduction in sacral and pudendal nerves [9]. The combination of the muscle and nerve impairment is suggested to cause a stiffer and smaller neorectum after radiotherapy [24], which can lead to a higher pressure in the neorectum even when just small

Table 3
Scores of EORTC QLQ-CR29.

	Mean score PRT + TME	Mean score TME	<i>P</i>
Body image	86.8	86.9	.87
Anxiety	84.1	80.4	.07
Weight	88.4	86.4	.17
Urinary frequency	29.9	28.4	.51
Urinary incontinence	14.6	12.8	.62
Dysuria	1.6	1.3	.39
Blood and mucus in stool	2.6	3.1	.57
Abdominal pain	5.2	6.6	.58
Buttock pain	10.7	6.8	.03
Bloating	8.5	11.8	.04
Dry mouth	17	19.7	.05
Hair loss	2.7	3	.83
Taste	4.8	4.3	.16
<i>Patients with stoma</i>			
Stool frequency	13.1	11.6	.67
Flatulence	21.6	18.8	.31
Faecal leakage	15.1	10	.08
Sore skin	12.3	8.7	.20
Embarrassment	9.6	11.2	.54
Stoma care problems	3.9	2.2	.17
<i>Patients without stoma</i>			
Stool frequency	26.3	19.4	.006
Flatulence	31.8	33.8	.43
Sore skin	22.5	10.1	<.001
Embarrassment	12.8	6.1	.04
Care problems	26.2	19	.09

Abbreviations: PRT, preoperative short-term radiotherapy; TME, total mesorectal excision.

Table 4
Urinary function and bowel function assessment.

	PRT + TME (%)	TME (%)	<i>P</i>
Involuntary urine loss	44.1	43.8	.89
Use of pads for urine loss during day and night	20.5	16.2	.05
Use of nappies for urine loss	4.2	4.7	.36
Stress incontinence	24.0	32.4	.05
Urge incontinence	27.9	26.9	.82
Combination of stress and urge incontinence	21.1	21.4	.94
Strong urge for defecation	78.7	60.9	.002
Defecation within 1 h of the last bowel opening	92.0	82.5	<.001
Anal mucus loss	29.9	14.4	.01
Pads for faecal leakage	57.7	34.4	.005

Abbreviations: PRT, preoperative short-term radiotherapy; TME, total mesorectal excision.

faecal volumes are involved. This results in a decreased capacity for the neorectum to act as a reservoir and consequently leads to more frequent defecation within 1 h and a higher stool frequency.

In this study, irradiated men reported to have more erection difficulties compared with non-irradiated men at 14 years after treatment, which confirms the previous analysis of this trial [23]. Sexual function of rectal cancer survivors was also assessed in a study of the Norwegian

Rectal Cancer Registry (NRCR). Patients were included if they had been treated with pre- or postoperative (chemo-) radiation or with surgery only, and at 5 years after treatment a higher prevalence of erectile dysfunction after radiation was found (86% in irradiated males versus 55% in non-irradiated males) [8]. With regard to females in the NRCR study, more vaginal dryness (50% after radiation versus 24% after surgery only), dyspareunia (35% versus 11%) and reduced vaginal dimension (35% versus 6%) were found after radiotherapy [7]. In the previous analysis of the TME trial 2 years after treatment, females reported problems with lubrication and dyspareunia after PRT + TME as well [23]. However, 14 years after treatment, no difference in vaginal dryness was found between the treatment arms. When comparing patients treated for rectal cancer with the Dutch population, all treated males reported less interest in sex, less sexual activity, decreased extent to which sex was enjoyable and more erection difficulties. Treated females also reported a decreased extent to which sex was enjoyable. Furthermore, irradiated females reported more vaginal dryness, and more pain at intercourse compared with the Dutch population. In the study using data from the Eindhoven Cancer registry, sexual function of patients 4 years after treatment was compared with the Dutch population. This study found results pointing in the same direction, but did find a difference in female sexual function and no difference in sexual enjoyment of males. However, no surgery only group was included in this analysis [25].

Despite the increased bowel symptoms and erection difficulties in male patients in the irradiated group, scores for general health status and functioning scales were not different from the non-irradiated group. This was also found in two other studies in, which patients were treated with surgery alone or with additional PRT [11,12]. When HRQL is compared between PRT + TME patients and patients who received preoperative (Polish trial) [26], or postoperative chemoradiation (MRC CR07/NCIC CTG C016) [27], no differences were reported either. In addition, previous analysis of the TME trial did not find differences in overall functioning and general health status between the treatment arms [23]. Possible explanations for why bowel and sexual dysfunction after PRT did not impact on general health status and functioning scores compared with TME are: firstly, patients adapt to their symptoms, especially 14 years after treatment; secondly, the impact of the symptoms is too small to have an effect on the more general functioning scales of the QLQ-C30.

In the Stockholm trials, more urinary incontinence was demonstrated in the PRT + surgery group [12], a finding that was not observed in our study. Because the Stockholm trials included a higher proportion of females (46.0%) compared to our study (41.2%), an additional analysis was performed in female patients,

Table 5
Sexual items of EORTC QLQ-CR38, EORTC QLQ CX24 and EORTC QLQ-PR25.

	Mean score PRT + TME	Mean score TME	<i>P</i> [*]	Δ PRT + TME – Norm	<i>P</i> [‡]	Δ TME – Norm	<i>P</i> [•]
<i>Male</i>							
Sexual interest	27.8	30.9	.27	−14.7	<.001	−12.9	<.001
Sexual activity	17.6	23.4	.04	−11.3	<.001	−6.6	.01
To what extent was sex enjoyable	54.8	53.1	.61	−8.7	.001	−10.8	<.001
Erection difficulties	72.4	55.7	.001	38.7	<.001	24.3	<.001
Ejaculation problems	59.4	48.6	.07				
Uncomfortable about being sexually intimate	44.6	31.5	.03				
<i>Female</i>							
Sexual interest	15.9	19.7	.59	−3.5	.19	−0.1	.68
Sexual activity	16.7	19.3	.76	1.6	.92	3.7	.48
To what extent was sex enjoyable	31.6	44.7	.08	−22.1	<.001	−9	.006
Vaginal dryness	35.8	24.2	.15	18.3	<.001	3.7	.08
Pain during intercourse	24.1	9.9	.04	20.8	<.001	3.4	.19
Vagina felt short/tight	25.6	15.4	.17				

Abbreviations: PRT, preoperative short-term radiotherapy; TME, total mesorectal excision; Norm, age and gender matched Dutch population. Higher scores for functioning indicate better functioning. For the symptom items, a higher score reflects a higher level of symptoms and decreased HRQL. A negative difference in functioning indicates worse functioning in the treatment arms and a positive difference for symptoms indicates a higher level of symptoms in the treatment arms compared to Norm.

* Difference between PRT + TME and TME.

‡ Difference between Norm and PRT + TME.

• Difference between Norm and TME.

which again did not find a difference between PRT + TME and TME. In the Stockholm trials, 32.4% of the patients were originally included in the Stockholm I trial. In this trial patients received preoperative radiotherapy (5 × 5 Gy) using a two-field technique. With this technique a larger part of the bladder is included in the radiation field compared to patients irradiated with a three or four-field technique. Other large randomised studies, which used the three or four-field technique, did not find major effects on the urinary function either [6,10].

As mentioned above, radiation technique is relevant for the risk of treatment-related toxicity. When irradiated volumes are reduced, adverse effects reduce as well, as can be seen when the TME trial is compared with the Stockholm I trial [28]. With the introduction of 3D-conformal radiotherapy and intensity-modulated radiotherapy, damage to adjacent healthy tissue can be minimised, which results in less acute bowel toxicity [29]. Although likely, it is not yet clear if these new radiation techniques also decrease long-term treatment-related toxicity. Therefore, optimal patient selection for radiotherapy is required, ensuring that only patients who are most likely to benefit from radiotherapy should receive this treatment. In addition, a recent trial found that bowel function could be improved with an intervention by a gastroenterologist or nurse during follow-up, compared to a self-help booklet [30]. This result shows that in the follow-up of patients treated for rectal cancer specific attention should be paid to functional outcome.

This very long-term HRQL analysis shows that 14 years after treatment for resectable rectal cancer, patients still experience negative effects of their

treatment. PRT + TME patients without stoma reported more bowel dysfunction than TME patients, and both treatment groups reported more sexual dysfunction than the norm population. Finally, both treatment arms showed a clinically small decrease in overall functioning and global health status compared to the norm population. These findings can be used to provide newly diagnosed rectal cancer patients with information about their possible long-term morbidity and health status after PRT + TME in order to make an informed decision about the risks and benefits of adjuvant radiotherapy.

Conflict of interest statement

None declared.

Acknowledgement

This work was supported by the Dutch Cancer Society (CKVO 95-04) and the Dutch National Health Council (OWG 97/026).

References

- [1] Enker WE. Total mesorectal excision – the new golden standard of surgery for rectal cancer. *Ann Med* 1997;29(2):127–33.
- [2] Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345(9):638–46.
- [3] Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet* 2009;373(9666):811–20.

- [4] Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;30(16):1926–33.
- [5] van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;12(6):575–82.
- [6] Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients – a Dutch colorectal cancer group study. *J Clin Oncol* 2005;23(25):6199–206.
- [7] Bruheim K, Tveit KM, Skovlund E, et al. Sexual function in females after radiotherapy for rectal cancer. *Acta Oncol* 2010;49(6):826–32.
- [8] Bruheim K, Guren MG, Dahl AA, et al. Sexual function in males after radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2010;76(4):1012–7.
- [9] Pollack J, Holm T, Cedermark B, Holmstrom B, Mellgren A. Long-term effect of preoperative radiation therapy on anorectal function. *Dis Colon Rectum* 2006;49(3):345–52.
- [10] Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol* 2005;23(34):8697–705.
- [11] Thong MS, Mols F, Lemmens VE, et al. Impact of preoperative radiotherapy on general and disease-specific health status of rectal cancer survivors: a population-based study. *Int J Radiat Oncol Biol Phys* 2011;81(3):e49–58.
- [12] Pollack J, Holm T, Cedermark B, et al. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. *Br J Surg* 2006;93(12):1519–25.
- [13] Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365–76.
- [14] Whistance RN, Conroy T, Chie W, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. *Eur J Cancer* 2009;45(17):3017–26.
- [15] Sprangers MA, te Velde A, Aaronson NK. The construction and testing of the EORTC colorectal cancer-specific quality of life questionnaire module (QLQ-CR38). European Organization for Research and Treatment of Cancer Study Group on Quality of Life. *Eur J Cancer* 1999;35(2):238–47.
- [16] Aaronson NK, vAG. EORTC Genitourinary Tract Cancer Group: An international field of the reliability and validity of the QLQ-C30 and a disease-specific questionnaire module (QLQ-PR25) for assessing quality of life of patients with prostate cancer: European Organization for Research and Treatment of Cancer study protocol (15011). Brussels, Belgium, European Organisation for Research and Treatment of Cancer.
- [17] Greimel ER, Kuljanic Vlasic K, Waldenstrom AC, et al. The European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life questionnaire cervical cancer module: EORTC QLQ-CX24. *Cancer* 2006;107(8):1812–22.
- [18] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 scoring manual. 2nd ed. Brussels, Belgium: European Organisation for Research and Treatment of Cancer; 1999.
- [19] van de Poll-Franse LV, Mols F, Gundy CM, et al. Normative data for the EORTC QLQ-C30 and EORTC-sexuality items in the general Dutch population. *Eur J Cancer* 2011;47(5):667–75.
- [20] Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16(1):139–44.
- [21] Lundby L, Krogh K, Jensen VJ, et al. Long-term anorectal dysfunction after postoperative radiotherapy for rectal cancer. *Dis Colon Rectum* 2005;48(7):1343–9, discussion 9–52; author reply 52.
- [22] Lundby L, Jensen VJ, Overgaard J, Laurberg S. Long-term colorectal function after postoperative radiotherapy for colorectal cancer. *Lancet* 1997;350(9077):564.
- [23] Marijnen CA, van de Velde CJ, Putter H, et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. *J Clin Oncol* 2005;23(9):1847–58.
- [24] Ziv Y, Zbar A, Bar-Shavit Y, Igov I. Low anterior resection syndrome (LARS): cause and effect and reconstructive considerations. *Tech Coloproctol* 2013;17(2):151–62.
- [25] Den Oudsten BL, Traa MJ, Thong MS, et al. Higher prevalence of sexual dysfunction in colon and rectal cancer survivors compared with the normative population: a population-based study. *Eur J Cancer* 2012;48(17):3161–70.
- [26] Pietrzak L, Bujko K, Nowacki MP, et al. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial. *Radiation Oncol* 2007;84(3):217–25.
- [27] Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials. Group C016 randomized clinical trial. *J Clin Oncol* 2010;28(27):4229–33.
- [28] Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer – a systematic overview. *Acta Oncol* 2007;46(4):504–16.
- [29] Samuelian JM, Callister MD, Ashman JB, Young-Fadok TM, Borad MJ, Gunderson LL. Reduced acute bowel toxicity in patients treated with intensity-modulated radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2012;82(5):1981–7.
- [30] Andreyev HJ, Benton BE, Lalji A, et al. Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. *Lancet* 2013;382(9910):2084–92.